AMENDMENTS TO THE DRAWINGS:

The attached sheet of drawings includes changes to Figure 9. Specifically, the "X" marks indicating recombination events have been replaced with single lines flanking either side (5' and 3') of the insert region.

REMARKS

Claims 1-7 and 16-18 are pending in this application. Without prejudice or disclaimer, claims 1, 3-7, and 16-18 are amended herein. No new matter has been added by these amendments.

Claims 3-5 are amended to replace the phrase "sequence number" with the term "SEQ ID NO:" and claims 6, 7, 16, and 17 are amended to correct an inadvertent typographical error in the spelling of Saccharomyces.

Claim 1 is amended to replace the phrases "incorporated by the promoter of the pyruvate decarboxylase gene" and "said promoter replaces said promoter" with the phrases "incorporated such that it is under the control of the promoter of the pyruvate decarboxylase gene" and "a structural and functional homologue of the promoter of the pyruvate decarboxylase gene, which replaces the promoter of the pyruvate decarboxylase gene on the host chromosome," respectively. Claim 16 is similarly amended. These amendments correct inadvertent grammatical errors made when translating the original Japanese-language specification. Support for these amendments can be found throughout the specification, *e.g.*, at page 6, lines 41-46; Example 4; and Figure 9.

PRIORITY

This application is a national stage entry of PCT/JP03/02833, filed March 11, 2003, which claims the benefit of Japanese Application No. 2002-065880, filed March 11, 2002. The Office contends, "[b]ecause an English translation of the foreign application JAPAN 2002-065880 has not been provided, the instant application has

been granted the benefit date, 3/11/2003, from the application PCT/JP03/02833 0." Office Action at p. 3.

Applicants respectfully traverse and submit herewith a certified English-language translation of Japanese Application 2002-065880. Accordingly, Applicants request that the Office acknowledge March 11, 2002, as the priority date of the instant application.

OBJECTION TO THE SPECIFICATION

The Office objects to the specification at pages 2-4, 6, 10, 11, 13, and 17, because "[t]here is no SEQ ID NO recited . . . when referring to the amino acid sequences and nucleic acid sequences." Office Action at p. 3. Applicants respectfully traverse.

The phrase "sequence number" on pages 2-4, 6, 10, 11, 13, and 17 of the specification refers to the corresponding SEQ ID NO in the Sequence Listing. Without acquiescing to the objection, Applicants herein amend the specification to replace the phrase "sequence number" on pages 2-4, 6, 10, 11, 13, and 17 with the term "SEQ ID NO." Accordingly, Applicants respectfully request that the objection to the specification be withdrawn.

OBJECTION TO THE DRAWINGS

The Office objects to the drawings because "Figure 9 includes crossed lead lines." Office Action at p. 4. Applicants respectfully traverse and submit that the Office is misinterpreting the "X" marks in Figure 9, which indicate recombination events, as "lead lines."

Notwithstanding, and without acquiescing to the objection, Applicants herein amend Figure 9 to remove the "X" marks indicating recombination events. Instead, the recombination events have been indicated by single lines flanking either side (5' and 3') of the insert region. Accordingly, Applicants respectfully request that the objection to the drawings be withdrawn.

CLAIM OBJECTIONS

Claims 6, 7, and 17 are objected to because "[t]he claims contain the word, 'Saccaromyces'. This is a typographical error; the correct spelling is 'Saccharomyces'." Office Action at p. 5. Applicants respectfully traverse.

Without acquiescing to the objection, claims 6, 7, 16[1], and 17 are amended herein to replace the term "Saccaromyces" with the term "Saccharomyces." Accordingly, Applicants respectfully request that the objection to claims 6, 7, and 17 be withdrawn.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112

A. Indefiniteness

Claims 1-7 and 16-18 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. *See* Office Action at pp. 5-6. Specifically, the Office contends that the phrases "incorporated by the promoter of the pyruvate decarboxylase," "said promoter that replaces said promoter," and "the aforementioned process" are unclear. *Id.* In addition, the Office contends that there is insufficient

[1] Although the Office did not object to claim 16, Applicants note that it also contains the term "Saccaromyces."

antecedent basis for the phrases "the bovine-derived lactate dehydrogenase" and "the promoter." *Id.* at p. 6. Applicants respectfully traverse.

Without acquiescing to the rejection, claim 1 is amended to replace the phrase "incorporated by the promoter of the pyruvate decarboxylase gene" with the phrase "incorporated such that it is under the control of the promoter of the pyruvate decarboxylase gene." Claim 16 is similarly amended. Claims 1 and 16 are also amended to replace the phrase "said promoter replaces said promoter" with the phrase "a structural and functional homologue of the promoter of the pyruvate decarboxylase gene, which replaces the promoter of the pyruvate decarboxylase gene on the host chromosome." Claim 18 is amended to replace the phrase "the aforementioned process" with the phrase "said process for culturing the transformant described in claim 1." Finally, claim 16 is amended to replace the term "the" with the term "a" in the phrases "the bovine-derived lactate dehydrogenase" and "the promoter."

Accordingly, Applicants respectfully request that the indefiniteness rejection of claims 1-7 and 16-18 be withdrawn.

B. Written Description

Claims 1-7 and 16-18 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. *See* Office Action at pp. 6-10. Specifically, the Office contends, "[c]laims 1 and 16 are broadly drawn, such that they apply to a genus of homologues of lactate dehydrogenase gene and homologues of pyruvate decarboxylase 1 promoters" and "[i]n addition, claims 1 and 16 are broadly drawn such that they encompass a genus of 'transformants.'" *Id.* at pp. 7 and 8. The Office concludes, "the disclosure is not sufficient to show that a skilled

artisan would recognize that the applicant was in possession of the claimed invention (genus) commensurate to its scope at the time the application was filed." *Id.* at p. 10. Applicants respectfully traverse.

An adequate disclosure of a claimed genus exists if an ordinary artisan could predict the operability in the invention of species other than the ones disclosed. *See* M.P.E.P. § 2163, 8th Edition, September 2007 Revision. Furthermore, what constitutes a sufficient disclosure of a representative number of species is an inverse function of the skill and knowledge in the art. *Id.* Given the inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement, information which is well known in the art need not be described in detail in the specification. *Id.*, (citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986)).

Regarding the genera of lactate dehydrogenase homologues and pyruvate decarboxylase promoters, the Office appears particularly concerned that the specification allegedly "does not describe which important structures must be included in the homologue in order to maintain function." Office Action at p. 8. However, the Office fails to consider that the level of skill and knowledge regarding lactate dehydrogenase genes and pyruvate decarboxylase promoters was high at the time the instant application was filed. As the attached *Li* and *Kellermann* evidentiary references illustrate, the correlation between structure and function for lactate dehydrogenase genes and pyruvate decarboxylase promoters was known in the art at the time the instant application was filed. *See, e.g., Li* at pp. 7022-23 and *Kellermann* at pp. 8969-73. Accordingly, Applicants respectfully submit that the specification provides adequate

support for the recited genera of lactate dehydrogenase homologues and pyruvate decarboxylase promoters in claims 1-7 and 16-18.

Regarding the genus of transformants, the Office contends that the specification allegedly does not provide sufficient species to establish that Applicants were in possession of transformants that are microbes, mold, animals, plants, or insects, as recited on page 1, paragraph [0002] of the specification. *See* Office Action at p. 8. Again, the Office fails to consider that at the time the instant application was filed, the level of skill and knowledge in the art regarding suitable hosts for gene transformation was high. The attached *Ausubel* and *Sambrook* evidentiary references illustrate that the skilled artisan knew of a variety of hosts for expressing recombinant proteins, including, *inter alia*, bacterial cells, insect cells, and mammalian cells. Thus, an ordinary artisan could readily predict that Applicants were in possession of the instantly claimed invention at the time the application was filed. Accordingly, Applicants respectfully submit that the specification provides adequate support for transformants comprising microbes, mold, animals, plants, and insects.

For at least these reasons, Applicants respectfully request that the written description rejection of claims 1-7 and 16-18 be withdrawn.

C. Enablement

Claims 16-17 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. *See* Office Action at pp. 10-14. Specifically, the Office contends, "the quantity of experimentation required to make and/or use the invention, as claimed, is insufficient to enable the invention." *Id.* at p. 14. Applicants respectfully traverse.

To satisfy the enablement requirement, the specification must enable a person of ordinary skill in the art to practice the claimed invention without undue experimentation. The Federal Circuit has held that making the claimed embodiments and screening them for function is acceptable, as long as the experimentation is not undue. Thus, the test is whether it would require undue experimentation to practice the invention. *See generally, Atlas Powder v. E.I. Du Pont de Nemours & Co.* 750 F.2d 1569, 224 U.S.P.Q. 409 (Fed. Cir. 1984). Furthermore, M.P.E.P. § 2164.06 states that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." M.P.E.P. § 2164.06 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)) (emphasis added).

The Office appears particularly concerned that the instantly claimed invention allegedly includes a large genus of pyruvate decarboxylase promoter homologues. *See* Office Action at pp. 11-13. For example, in analyzing the "nature of the invention" the Office states that the instantly claimed invention "is obviously generic to a considerable number of nucleotides varying in the length of the nucleic acids, the degree of homologies among the sequences, and the biological activities of the encoded polypeptides, which may or may not be involved in the function of Saccharomyces cerevisiae pyruvate decarboxylase 1 promoter." Office Action at p. 12. Likewise, in discussing the "working examples and guidance provided" the Office states, "[t]he specification indicates that any DNA which hybridizes to SEQ ID NO:2 could be considered a homologue of the Saccharomyces cerevisiae pyruvate decarboxylase 1

promoter (parag. 0024)." Office Action at p. 12. Finally, in addressing the "state of the art and analysis of the issues" the Office concludes, "[s]ome of the nucleic acids that fit within the genus of Claim 16 would not be homologues of Saccharomyces cerevisiae pyruvate decarboxylase 1 promoter (SEQ ID NO:2). In fact, despite hybridizing under high stringency conditions, these molecules would be structurally and functionally unrelated to Saccharomyces cerevisiae pyruvate decarboxylase 1 promoter (SEQ ID NO:2)." *Id.* at pp. 12-13.

Applicants respectfully submit that the Office's analysis of the individual *Wands* factors appears to rely on a misconception regarding the term "homologue" in claim 16. Specifically, the Office's discussion fails to consider that page 6, lines 40-46 of the specification teach:

> For the promoter segment in the present DNA structure, it is possible to use a DNA comprised of the base sequence described in sequence number 2, as well as a DNA that is comprised of this base sequence with one or several bases void, replaced, or added, **and which has promoter activity**; or a DNA that is hybridized with a DNA formulated from some or all of the sequences in the base sequence shown in sequence number 2 or its complementary strand under stringent conditions **and which has promoter activity** (in other words, the homologue of said promoter).

(Emphasis added). Thus, the specification does not teach that *any* DNA which hybridizes to SEQ ID NO:2 could be considered a homologue of Saccharomyces cerevisiae pyruvate decarboxylase 1 promoter, as alleged by the Office in the "working examples and guidance provided" section on page 12 of the Office Action. Rather, the DNA must retain pyruvate decarboxylase 1 gene promoter activity. Accordingly, claim 16 does not read on homologues that are structurally and functionally unrelated to the

Saccharomyces cerevisiae pyruvate decarboxylase 1 promoter, as alleged by the Office in the "nature of the invention" and "state of the art and analysis of the issues" sections on pages 11-14 of the Office Action. Moreover, since claim 16 expressly recites "a homologue" of the promoter of the pyruvate decarboxylase gene, it does not read on nucleic acids that are not homologues of the Saccharomyces cerevisiae pyruvate decarboxylase 1 promoter, as alleged by the Office in the "state of the art and analysis of the issues" section on pages 12-14 of the Office Action.

In addition, the Office's analysis of the *Wands* factors fails to consider the specific working examples and guidance provided in the specification for making and using the instant invention. For example, Figures 3-9 and 14-15 and Embodiments 3 and 4 on pages 10-13 of the specification provide detailed instructions of exemplary cloning schemes for making and using the instantly claimed invention. These examples, along with the definition of pyruvate decarboxylase promoter homologues provided on page 6, lines 40-46 of the specification provide adequate guidance to enable one skilled in the art to practice the instantly claimed invention.

Notwithstanding, Applicants have amended claim 16[2] to recite "a structural and functional homologue of the promoter of the pyruvate decarboxylase gene" to expressly eliminate inoperable embodiments. Accordingly, Applicants respectfully request that the enablement rejection of claims 16 and 17 be withdrawn.

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[2] Although the Office did not reject claim 1 under enablement, Applicants have also amended claim 1.

CLAIM REJECTIONS UNDER 35 U.S.C. § 102

Claims 1-4, 6-7, and 16-18 are rejected under 35 U.S.C. §§ 102(b) and (e) as allegedly being anticipated by U.S. Patent No. 6,429,006 or WO 99/14335 to Porro et al. ("*Porro*"). Office Action at pp. 15-18. Specifically, the Office contends, "Porro et al. teach, 'a process for the preparation of . . . lactic acid by culturing the above described metabolically engineered yeast strains in a fermentation medium containing a carbon source and recovering lactic acid from the fermentation medium' (col.2, lines 54-58). Therefore Porro et al. anticipated the instant claims." *Id.* at p. 18. Applicants respectfully traverse.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131 (quoting *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)) (emphasis added). Further, a rejection under § 102 is proper only when the claimed subject matter is identically described or disclosed in the prior art. *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972) (emphasis added). The identical invention must be described in as complete detail as is contained in, and must be arranged as required by, the claim. M.P.E.P. § 2131.

Applicants submit that *Porro* cannot anticipate the instantly claimed invention because it fails to teach "the DNA for coding the aforementioned foreign protein [a bovine-derived lactate dehydrogenase or it's homologue] has been incorporated such that it is under the control of the [a] promoter of the pyruvate decarboxylase [1] gene on the host chromosome [of the Saccharomyces family], or such that it [the DNA] is under the control of a structural and functional homologue of the promoter of the pyruvate

decarboxylase gene, which replaces the promoter of the pyruvate decarboxylase gene on the host chromosome," as required by independent claims 1 and 16.

The instantly claimed invention requires that the DNA encoding lactate dehydrogenase is incorporated into the downstream (3') side of the pyruvate decarboxylase gene promoter on the host chromosome. Applicants discovered that the instant invention advantageously produces large volumes of lactic acid while simultaneously destroying the pyruvate decarboxylase gene that suppresses the production of lactic acid. *See*, *e.g.*, paragraphs [0026], and [0027] of the specification. Embodiment 5 in the specification demonstrates that "[e]ven though only a single copy of the LDHKCB gene had been incorporated into each of the transformants . . . production of between 4.5 and 5.0% (45.0 to 50.0 g) of L-lactic acid was confirmed in each 1 L of the culture solution." Specification at p. 14, ll. 3-5. In contrast, Tables 3A and 3B of *Porro* reveal that the transformants disclosed therein, which express the LDH gene from an exogenous a 2μm plasmid, produce less lactic acid, even after the transformants have been manipulated to enhance production by reducing the PDC activity or increasing the LDH gene copy number (Table 3B). Unlike *Porro*, lactic acid can be efficiently produced by the instantly claimed invention with only a single copy of the LDG gene and without suppression of pyruvate decarboxylase.

For at least these reasons, Applicants submit that the instantly claimed invention is novel over *Porro*. Accordingly, Applicants respectfully request that the rejection of claims 1-4, 6-7, and 16-18 are rejected under 35 U.S.C. §§ 102(b) and (e) be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: November 20, 2007

By: Amanda K. Murphy
Amanda K. Murphy
Reg. No. 59,387

Attachments:

A certified English translation of JP 2002-065880; and

One Replacement Drawing Sheet to replace Figure 9.